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The impact of stroke hemispheric location and age on acute ischemic stroke assessment with the NIH stroke scale

Rita Carrilho Pichel

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RESUMO

Contexto e objetivos: A avaliação correta e atempada do acidente vascular cerebral (AVC) é essencial para a estratificação dos doentes para tratamento. A escala de AVC da NIH (NIHSS) é a primeira ferramenta a ser aplicada, e a pontuação da mesma pode ser influenciada pela localização do AVC e pela idade do doente, quando ajustada para o tamanho da lesão. Por esse motivo, pretendemos avaliar o impacto da localização hemisférica do AVC e da idade do doente na pontuação da *NIHSS*. Por fim, propomos criar uma pontuação da *NIHSS* corrigida que avalie melhor o tecido cerebral em risco, independentemente da localização hemisférica.

Métodos: Analisámos a pontuação total da *NIHSS* obtida no serviço de urgência do Hospital de Santo António do Centro Hospitalar do Porto entre janeiro de 2015 e junho de 2017 e determinámos o *Alberta Stroke Program Early CT Score* (*ASPECTS*) do estudo de perfusão. Avaliámos, então, o efeito da localização hemisférica e da idade do doente na pontuação da *NIHSS* e no *ASPECTS*. Com base na pontuação da *NIHSS* discriminada, desenvolvemos e testamos a *NIHSS-corrigida* (*c-NIHSS*).

Resultados: Nesta coorte retrospetiva de 228 doentes com AVC isquémico agudo não-lacunar da circulação anterior verificámos que os casos de AVC do hemisfério direito pontuaram menos na *NIHSS* do que os do hemisfério esquerdo (P=0.048), apesar de a extensão do território hipoperfundido determinada pelo *ASPECTS* ser maior nos primeiros (P=0.004). As diferenças na pontuação da *NIHSS* entre AVC direito e AVC esquerdo foram significativas nos doentes com maior hipoperfusão e nos doentes com oclusões mais proximais. A pontuação na *NIHSS* foi maior nos doentes mais velhos (P=0.001) e a área hipoperfundida nos doentes com AVC direito foi maior dentro do grupo de doentes ≤75anos, comparativamente com os doentes da mesma idade com AVC esquerdo (P=0.027). Ao usarmos a pontuação da *c-NIHSS*, as diferenças entre AVC esquerdo e AVC direito deixam de existir.

Conclusões: A pontuação da *NIHSS* subestima o tecido cerebral em risco no AVC do hemisfério direito. Para além disso, a pontuação da *NIHSS* correlaciona-se positivamente com a idade e as diferenças relacionadas com o lado do AVC são mais evidentes nos doentes mais novos. A *c-NIHSS* pode constituir uma ferramenta mais equilibrada para a avaliação do AVC agudo.

LISTA DE ABREVIATURAS

ASPECTS: Alberta Stroke Program Early Computed Tomography Score

CBF: cerebral blood flow

CBV: cerebral blood volume

CHP: Centro Hospitalar do Porto – Oporto, Portugal.

CTA: computed tomography angiography

CTP: computed tomography perfusion

C-NIHSS: *corrected* National Institutes of Health Stroke Scale

ICA: internal carotid artery

IV rtPA: intravenous recombinant tissue plasminogen activator

LHS: left hemisphere stroke

M1: middle cerebral artery M1 segment

M2: middle cerebral artery M2 segment

M3: middle cerebral artery M3 segment

MCA: middle cerebral artery

MTT: mean transit time

NIHSS: National Institutes of Health Stroke Scale

RHS: right hemisphere stroke

rtPA: recombinant tissue plasminogen activator

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Abstract

Background and Purpose: Timely and accurate stroke assessment is essential for patient stratification for treatments. NIH stroke scale (NIHSS) is the first tool to implement and its score may be influenced by stroke location or patient age, when adjusted for lesion size. For that purpose, we aimed to evaluate the impact of stroke hemispheric location and patient`s age on NIHSS score. Ultimately, we will generate a corrected NIHSS that would best evaluate brain tissue at risk, independently of its hemispheric location.

Methods: We analyzed NIHSS total score obtained in the emergency department of Hospital de Santo António, Centro Hospitalar do Porto, between January 2015 and June 2017, and assessed Alberta Stroke Program Early CT Score (ASPECTS) in CT perfusion. We evaluated the effect of hemispheric location and patient's age in NIHSS and ASPECTS. We developed and tested the *corrected*-NIHSS (*c-NIHSS*) based on discriminated NIHSS scores.

Results: In this retrospective cohort of 228 patients with non-lacunar acute ischemic stroke of the anterior circulation we found that right hemisphere stroke (RHS) scored less in NIHSS compared to left hemisphere stroke (LHS) ($P=0.048$), even though the extension of hypoperfused territory assessed by ASPECTS was higher ($P=0.004$). NIHSS score differences between RHS and LHS were significant in patients with ASPECTS≤3 ($P<0.001$) and with ICA ($P=0.048$) or M1 occlusions ($P=0.007$). NIHSS score was higher in older patients ($P=0.001$), and RHS hypoperfused area was bigger within the group of ≤75y, compared to same-aged patients with LHS ($P=0.027$). When we used the *c-NIHSS* score, between-LHS and RHS differences ceased to exist.

Conclusions: NIHSS score underestimates the brain tissue at risk in right-hemisphere strokes. Moreover, NIHSS positively correlates with age, and stroke side-related differences are more evident in younger patients. The *c-NIHSS* may constitute a more balanced tool for acute stroke assessment.

Introduction

Stroke is the major cause of death in Portugal and the second leading cause of death worldwide.[1, 2] Global burden of stroke has increased in terms of absolute number of people affected by it or who remained disabled from it.[3] Still, the efforts made in stroke prevention and early management, like implementation of acute stroke units, thrombolysis and thrombectomy, have improved patient outcome and have resulted in a significant decline in age-standardized stroke prevalence and death, and disability-adjusted life years due to stroke.[4] This is largely dependent of a timely diagnosis and of a adequate stratification of stroke patients in the emergency setting. For that purpose the NIH stroke scale (NIHSS) constitutes a very important tool.

The NIHSS is a standard and reliable measure of the neurological deficits, recommended to be used in the emergency department to access stroke severity.[5, 6] Baseline NIHSS score is important for selecting patients for thrombolysis or thrombectomy, as it correlates with lesion volume, large vessel occlusion and it predicts stroke outcomes and patients prognosis.[7-9] These correlations are more significant for anterior circulation and non-lacunar strokes within the first hours of symptoms.[8-11] However, studies comparing left hemisphere stroke (LHS) with right hemisphere stroke (RHS) have demonstrated that the baseline NIHSS underestimates the RHS severity. Thus, for similar clinical stroke severity accessed by baseline NIHSS scores, in RHS (compared to LHS): infarction volume and post-thrombolysis hemorrhage rates are higher, prognosis is worst and the range of improvement after treatment is narrower.[12-14] This is of more concern in less differentiated hospitals, where patient assessment may not be done by neurology or stroke specialists, and the interpretation of NIHSS may be done literally, undervaluing stroke patient lesions in right hemispheric stroke.

So, refining the clinical standardized evaluation to match the amount of tissue at risk for infarction would probably contribute to better patient stratification for treatment and to define prognosis.

The use of the NIHSS in older patients' selection for treatment also raises concerns regarding the influence of age in the clinical assessment using the NIHSS. It is conceivable that stroke severity could be overestimated in older patients, due to previous age-related clinical and sub-clinical neurological deficits. In fact, severe leukoaraiosis is shown to attenuate NIHSS differences between LHS and RHS relating to higher NIHSS scores of components historically assigned to dominant hemisphere function.[15]

Having that in mind, in the present study, we aimed to: (i) evaluate the influence of stroke hemispheric location (LHS vs. RHS) on the NIHSS score in the acute setting; (ii) assess the influence of age on the NIHSS score; and (iii) generate a corrected-NIHSS score to minimize differences related to stroke hemispheric location.

Methods

We selected a consecutive series of patients with non-lacunar acute ischemic stroke of the anterior cerebral territory that were evaluated in our centre, Hospital de Santo António, Centro Hospitalar do Porto (CHP), between January 2015 and June 2017. Our sources were the Neurorradiology department CTP registries and the Neurology department Stroke Unit inpatients database.

Patients were potentially eligible for the study if they were referred to our centre, had performed CTP and met the following inclusion criteria: (1) nonlacunar acute ischemic stroke of the anterior cerebral territory, as shown on the imaging study; (2) baseline NIHSS total score obtained by a neurologist at hospital admission and registered on either the patient physical file or e-record; (3) computed tomography angiography (CTA) and CTP performed after the clinical evaluation in the same hospital. Exclusion criteria were: missing data of the NIHSS total score; previous modified Rankin Scale > 3; negative imaging study or other diagnosis than acute ischemic stroke; concomitant intracranial lesions that could mimic the neurological deficits; previous stroke involving more than one third of middle cerebral artery (MCA) territory on CT; watershed stroke (due to cardiogenic cause or cervical occlusion without intracranial occlusion); posterior circulation stroke; and lacunar stroke (exclusively).

Information obtained from patients´ clinical files included: demographics, origin (from ambulatory or transferred from other hospitals), time of symptom onset (defined by the time the patient was "last seen to be well"), total NIHSS score, the score of each item of the NIHSS, time of neurological examination (last evaluation before CTP), time of CTP and treatment (thrombolysis and/or thrombectomy) and, in the case of transferred patients, we registered pre-admission treatment done in the referring hospital. Ethnicity and handedness weren't collected, as they weren't systematically registered in patients' files.

This study was authorized by the local Ethics Commission.

Corrections to NIHSS score

Each item score was collected from patients with discriminated NIHSS score, as well as the presence of asomatognosia in the neurologic examination registry. Based on this information, we created the *c-11* item. In order to match the item 9 maximum score, patients with asomotognosia scored 3 points in *11-c* and all other patients scored the same as in item 11 of the NIHSS. Thus, both items 9 and *c-11*, which, respectively, assess dominant and non-dominant hemispheres dysfunction, would range from 0 to 3 points.

Finally, a corrected NIHSS (*c-NIHSS*) was calculated by the sum of items 1a, 2 to 10 and *c-11*. The reason for not including items 1b and 1c in the *c-NIHSS*, was to balance LHS and RHS potential points since 1b instructions tell us to attribute 2 points (maximum score) for aphasia and 1c depends on comprehension, even though pantomime could overcome communication barriers, giving LHS 4 potential extra points compared to RHS.

Imaging protocol

All patients had a non-contrast CT and a CTA (aortic arch to vertex). CTP studies were performed on two multidetector helical scanners (64 section LightSpeed GE Healthcare, Milwaukee, WI, USA and 16 section Brilliance Philips Healthcare, Best, The Netherland.) as a 45-second cine series, after power injection of 50ml of iodinated contrast at 4ml/s. The study range included at least one image at the level of the basal ganglia and at least one image above the basal ganglia.

Image analysis

CTP studies were post-processed by using a standard deconvolution, commercially available, software package (CTP3 “Std”, GE Heathcare and Brain CT Perfusion Package, Philips Healthcare, respectively), obtaining cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit times (MTT) parametric, color-coded maps.

The principles of ASPECTS scoring for CTP studies have been described elsewhere.[16] Briefly, the affected MCA territory was divided in ten regions through two axial planes (those described above), each scoring one point. Each region was classified as normal or abnormal (i.e., hypoperfused), as compared to the contralateral side; if abnormal, one point was deducted. Thus, a score of 10 indicated a completely normal study and a score of 0 indicated complete MCA territory hypoperfusion.

MTT and CBF maps were used to assess hypoperfusion; CBV maps and non-contrast CT were used to assess established infarction at presentation.[17] The presence of CTP mismatch or significant salvageable penumbra was considered whenever the extension of the hypoperfused area was twice the extension of the established infarction.

Non-contrast CT, CTA and CTP recorded acquisitions were reviewed by neuroradiologists (AC and HD) blinded from the clinical data, namely NIHSS score. Stroke hemispheric location (LHS or RHS), subtype of stroke (lacunar or *non-lacunar*), presence and site of artery occlusion, presence of tandem (simultaneous cervical and intra-cranial occlusion), CTP ASPECTS and presence of mismatch were determined by consensus.

In 29 candidates, who had performed CTP in the other tertiary hospital from Porto before being transferred to CHP, we analyzed CTA and CTP acquisitions from that hospital and also the NIHSS score previous to CTP.

<u>Statistical analysis</u>

Unless otherwise stated, continuous variables are reported as median (interquartile range) and categorical variables are reported as count or percentage. For continuous variables, assumption of non-normal distribution was assessed with Shapiro-Wilk test, between-group comparisons were done using Mann-Whitney U test and correlations were tested with Spearmann’s correlation coefficient. For categorical variables between-group comparisons we used Chi-square test or Fisher’s exact test, when appropriate.

In order to further characterize stroke hemispheric location impact, patients were stratified according to NIHSS score in 5-points strata, as in previous studies[12, 18] We also stratified NIHSS score according to the hypoperfused area, in two groups, with ASPECTS smaller or greater than the median value, and according to the site of arterial occlusion.

Concerning age impact, patients younger and older than 75 years were compared. This cut-point was chosen because it was close to median age and it was used before.[19] Additionally, NIHSS score was analyzed by stroke hemispheric location and by age groups.

To test corrections to NIHSS, a subgroup analysis of patients with discriminated NIHSS score was performed using *c-NIHSS* score. IBM SPSS Statistics 23 software was used for the statistic analysis.

Results

In this retrospective cohort study we identified 508 potential eligible patients, who had performed CTP or thrombectomy at the hospital between January 2015 and June 2017. Out of these we selected 118 LHS and 110 RHS non-lacunar acute ischemic stroke cases of the anterior cerebral territory that fulfilled the selection criteria. Reasons for patient exclusion are depicted in figure 1.

Patients that had been submitted to IV rt-PA were younger and presented longer time from symptom onset to NIHSS and to CTP and shorter time from NIHSS to CTP compared to non-treated patients. No other relevant differences were found, namely in NIHSS score or neuroimaging parameters (supplemental table 1).

There were no differences between patients with RHS or LHS regarding demographics, time until clinical or neuroimaging assessment and neuroimaging characteristics (as mismatch and site of arterial occlusion) (table 1). However, as expected, patients with RHS had a lower NIHSS score compared to LHS (P=0.048), even though the extension of hypoperfused territory assessed by ASPECTS was higher (P=0.004). This lower ASPECTS (larger hypoperfused area) in RHS compared to LHS was evident even within the time window for thrombolysis (onset-to-CTP time ≤ 270 minutes) [3(1-5) vs. 4(3-7), P=0.002] (figure 2).

When we analyzed ASPECTS by stroke location, within each NIHSS score stratum, RHS had a significantly lower score (bigger hypoperfusion area) than LHS, in 6 to 10 points (P=0.003) and in 11 to 15 points categories (P=0.044). Curiously, median ASPECTS of RHS was approximately equal to the median ASPECTS of LHS in the following NIHSS 5-points category (table 2).

Consistently, when we compared ASPECTS by stroke location, within each ASPECTS stratum and site of occlusion, NIHSS score was significantly higher for LHS than for RHS in patients with bigger hypoperfused area (ASPECTS<=3) (P<0.001) and in patients with proximal occlusions [ICA (P=0.048) and M1 (P=0.007)] (table 3).

The NIHSS score and the ASPECTS were negatively correlated (r_s=-0.358, P<0.001) with a higher negative correlation coefficient for LHS versus RHS (r_s=-0.491 vs. r_s=-0.264, P=0.023) (supplemental table 2).

NIHSS score was correlated with age (r_s=0.192, P=0.004). NIHSS score was higher in older patients compared to patients younger than 75 years, regardless of the stroke hemispheric location, and these findings did not seem to be related to the extent of hypoperfused brain territory, because we did not find differences in the ASPECTS between the two age groups (table 4). Within each age group, the NIHSS score did not differ between LHS and RHS, but RHS had lower ASPECTS compared to LHS, in patients younger than 75 years [3(1-5) vs. 4(2-7), P=0.027] but not in older patients.

Discriminated NIHSS score was available in 121 (53.1%) patients, 64 LHS and 57 RHS. We did not find differences between these patients and those without the discriminated NIHSS score, except for the proportion of patients that underwent thrombectomy, which was higher in patients with discriminated NIHSS score, compared to those without it (77,7% vs. 47,7%, P<0.001). Within the group of discriminated NIHSS score, the difference in the NIHSS score between LHS and RHS did not reach statistical significance and LHS had more tandem lesions than RHS (P=0.013). Similarly to the global sample, in this subsample, RHS had lower ASPECTS (bigger ischemia) than LHS (P=0.011) and we did not find differences between LHS and RHS patients for the remaining variables (supplemental table 3). ASPECTS was lower for RHS than LHS in 6 to 10 points stratum (P=0.026) and in 11 to 15 points stratum (P=0.018); and the NIHSS score was higher for LHS than for RHS in patients with bigger hypoperfused area (P=0.022) and with M1 occlusions (P=0.026) but not in patients with ICA occlusions, probably because of lower counts.

When we applied the proposed corrections to the NIHSS, the differences in the *c-NIHSS* score between LHS and RHS ceased to exist (supplemental table 3). Analyzing by stratified *c-NIHSS* score, ASPECTS was lower for RHS than LHS in 11 to 15 points stratum (P=0.014), but not in 6 to 10 points stratum (table 2). Also, we did not find differences in *c-NIHSS* score by stroke hemispheric location in patients with bigger hypoperfused area and in patients with M1 occlusion (table 3). ASPECTS correlation with *c-NIHSS* and with NIHSS scores in this subset of patients by stroke hemispheric location are available on supplemental table 2. We did not find statistically significant hemispheric differences in these correlation coefficients.

The NIHSS items scores by stroke hemispheric location are described in supplemental table 4. LHS patients scored more than RHS in items 1b (Level of conscience questions), 1c (Level of conscience commands) and 9 (Best language) ($P<0.001$) and the percentage of patients that scored in 1b or 1c was higher in LHS than in RHS (84.4% vs. 31.6%, $p<0.001$). RHS patients scored more than LHS in items 2 (Best gaze) ($P<0.001$), 5 (Motor arm) ($P=0.047$) and 11 (Extinction and inattention) ($P<0.001$). None of the patients with LHS scored more than 20pts in the *c-NIHSS*.

Discussion

In the *era* of thrombolysis and thrombectomy, recognizing stroke patients and valuing their deficits and the corresponding amount of brain tissue at risk is essential to provide the adequate treatment and minimize stroke related incapacity. Having that in mind, in our study, we addressed this matter and found that stroke severity assessed by NIHSS score was lower in RHS than in LHS, even though RHS patients had larger hypoperfused area (lower CTP ASPECTS score for CBF and MTT) compared to LHS patients. This study shows such asymmetry within time window for thrombolysis and highlights the importance of considering hemispheric stroke location when appreciating the absolute score of NIHSS. Previous studies have shown comparable results: in a series of stroke patients at late stages, for a given baseline NIHSS score, lesion volume on 3-months NCCT was higher for RHS patients than for LHS patients, and Fink *et al* described a trend for the NIHSS score to be lower in RHS than in LHS in a series of acute stroke patients, when adjusted for acute lesion volume on DWI and PWI.[12, 18]

Hemispheric comparison of the hypoperfused area within NIHSS score strata showed that the ASPECTS tended to be lower in RHS than LHS (in a consistent way, although not statistically significant in all strata), meaning bigger perfusion abnormalities in RHS than LHS for equivalent NIHSS scores. This was particularly clear in NIHSS strata 6-10 and 11-15. Possible reasons for we not having reached statistical significance in other strata are: small subgroup counts, as in the first stratum (0-5pts), and small ASPECTS range for CTP-CBF and MTT in more severe strokes (16-20pts; >20). Interestingly, alike *Woo et al*, we noticed that the median ASPECTS of RHS in a stratum was approximately equal to the median ASPECTS of LHS in the next-highest stratum. This is concordant with the empirical 5 points difference in the potential points between LHS and RHS, and with previous findings of 4 points difference in the NIHSS score between LHS and RHS.[12, 13]

When we stratified patients by ASPECTS and by site of occlusion, we found that the stroke severity assessed with NIHSS was overestimated in LHS, compared to RHS, in patients with bigger perfusion deficits and with proximal occlusions.

The finding that stroke severity assessment with NIHSS underestimates perfusion changes in RHS was expectable, considering the smallest weight of right hemisphere function (extinction/ inattention) that account for 2 possible points in the NIHSS compared to left hemisphere function (aphasia) that accounts for 7 possible points: not only in language item 9, but also in level of conscience items 1b and 1c, that depend on preserved language. Brott *et al* justified supplementing the scale with these two items (from the Edinburgh-2 coma scale) to increase reliability and sensitivity of level of conscience assessment.[5, 20] But, in the study that validated the scale, 8% of the patients were considered "not testable" in items 1b and 1c, which is consistent to Goldstein *et al* instructions to code items as "untestable" when appropriated.[5, 21] Current versions of the scale have more explicit instructions for these items, which can improve inter-observers concordance but create a systematic overestimation of LHS severity.[22]

Concerning age related impact on the NIHSS score, we found a positive correlation between NIHSS score and age, and patients with 75 years old or more had higher NIHSS score, as previously described, independently of stroke lateralization.[19]

Based on the recent finding of leukoaraiosis attenuation of stroke hemispheric location difference, and on empiric knowledge of age related deficits typically are more assigned to dominant hemisphere function, it was expected that age could overrate RHS severity, counterbalancing the hemispheric lateralization of the NIHSS.[15] In this study, although we did not find differences in NIHSS score between LHS and RHS within each age group, the RHS hypoperfused area was bigger within the group of patients with less than 75 years old, compared to same-aged patients with LHS. These findings mean that in younger patients stroke side-related inequalities are more evident, and they vanish with age, like anticipated.

Although the differences in the NIHSS score between LHS and RHS in the subset of patients with discriminated NIHSS score were not significant they exhibited the same tendency as the whole series: LHS scored more than RHS despite RHS had lower ASPECTS (bigger ischemia). Not surprisingly, LHS had significantly higher scores, not only in item 9, but also in level of conscience items 1b and 1c, thus supporting its elimination from the scale to overcome differences in the assessment of stroke severity between stroke-hemispheres. RHS had higher scores in items 2 (best gaze) and 5 (motor arm), beside item 11. This can be attributed to bigger hypoperfusion area in RHS than LHS. Also, gaze palsy scoring can be due to a confounding effect of neglect (more likely to mimic deficits in RHS).[13]

On the other hand, *c-NIHSS* score was not different between LHS and RHS and it tended to be higher in RHS than LHS, as the ischemia was higher in RHS than in LHS. Also, it was not different between LHS and RHS within the categories of bigger hypoperfusion and proximal occlusions. These findings suggest that *c-NIHSS* can be a promising solution for the overestimation of LHS severity with NIHSS. Nevertheless, it needs to be prospectively validated before its implementation.

Our study has some limitations, like a potential selection bias, which left very-mild and very-severe stroke patients out, because they were not candidates for thrombectomy, and for this reason they did not undergo CTP and did not meet inclusion criteria. Thus, in our study, the global median of the NIHSS score was high and the range of NIHSS scores was narrow. Another potential limitation of our study was the globally *low* negative correlation (*moderate* for LHS and *negligible* for RHS) of the NIHSS score with the ASPECTS for CTP, possibly because of semiquantitative nature of ASPECTS score.[23]

Still, the absolute value of the correlation between semi-quantitative perfusion abnormalities and the NIHSS score (r_s=-0.36) was similar to that initially reported by *Brott et al* for baseline lesion volume on NCCT (r=0.39). Also, it was consistent with previously reported correlation coefficients of the NIHSS score with the volume of hypoperfusion measured by PWI-MR, and with infarction volume from 30-day CT (r=0.37) in a population of large hemispheric strokes. [13, 24] On the other hand, Furtado *et al* did not find overall significant difference in terms of correlation with clinical scores between these methods of semiquantitative imaging (namely, ASPECTS) and quantitative methods. Moreover, within semiquantitative parameters, the best correlation with the admission NIHSS score was described for ASPECTS of MTT (r_s=0.78) and CBF (r_s=0.65) maps, which was assessed in our study.[25] So, the low correlation between the CTP-ASPECTS and the NIHSS score in our study can also be explained by the inter-rater variability, once we had many observers applying the NIHSS, even though they were neurologists of a stroke team, previously involved in NIHSS online training programs.

Contrasting findings exist about the hemispheric dependent differences of NIHSS score correlation with lesion volume. Brott *et al* and Woo *et al* found equal correlation coefficients, independently of stroke hemispheric location.[5, 12] More recent studies described lower correlation in RHS weighted against LHS, in line with our results.[18, 24, 25] *C-NIHSS* score did not correlate better with perfusion changes than NIHSS score, specifically in RHS, probably because asomatognosia is not necessarily representative of larger lesions than other extinction or inattention problems, although it results in worst outcomes. Other cognitive assessments could increase this correlation, but it was not possible to accomplish in this retrospective study and holds limitations in the acute stroke settings.[24]

Clinical relevance of our study is highlighted by previous studies analyzing stroke outcome that concluded that RHS had less favorable outcome than LHS, if adjusted for NIHSS score.[14, 26-30]

In conclusion, our study shows that the differences between left- and right-hemisphere strokes are already evident in the early stage of a stroke, when the brain lesion is not yet established and in time for an acute therapeutic intervention. This is particularly evident in younger patients, with larger cerebral hypoperfusion or with more proximal intracranial arterial occlusions. It calls for the attention of emergency physicians for them not to undervalue RHS based on NIHSS and thereby exclude them from treatment. On the other hand, LHS are overvalued by NIHSS and eventually patients could be excluded from treatment if only such an assessment is taken into account. Therefore, the development of an integrated model to assess stroke severity is essential, involving not only NIHSS score or *c-NIHSS* score, but also stroke hemisphere, patient's age and, additional disease biomarkers to optimize patient stratification for treatment.

Summary

In our population of non-lacunar acute ischemic strokes of the anterior circulation, NIHSS score overestimated the acute perfusion changes in left- compared to right-hemisphere stroke patient and we have found that patients with bigger right hemisphere hypoperfusion and more proximal occlusions have lower scores in NIHSS compared to equally sized left sided strokes. Moreover, NIHSS was positively correlated with age, independently of stroke hemispheric location. Our *c-NIHSS* seems a promising tool to equally estimate tissue at risk in left- and right-hemisphere stroke patients. Still, deeper exploratory items analysis and prospective studies are needed.

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References

1. Causas de morte 2015. INE Statistics Portugal. 2017. https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_publicacoes&PUBLICACOESpub_boui=277099566&PUBLICACOESmodo=2. Accessed February 19, 2018.

2. The top 10 causes of death 2015. WHO GHO. 2017. http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed May 15, 2018.

3. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circulation research*. 2017;120:439-448

4. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al. Global, regional, and national burden of neurological disorders during 1990–2015: A systematic analysis for the global burden of disease study 2015. *The Lancet Neurology*. 2017;16:877-897

5. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 1989;20:864-870

6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018:STR.0000000000000158

7. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono M-L, et al. National institutes of health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke*. 2013;44:1153-1157

8. Adams HP, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline nih stroke scale score strongly predicts outcome after stroke: A report of the trial of org 10172 in acute stroke treatment (toast). *Neurology*. 1999;53:126-131

9. Fonarow GC, Saver JL, Smith EE, Broderick JP, Kleindorfer DO, Sacco RL, et al. Relationship of national institutes of health stroke scale to 30-day mortality in medicare beneficiaries with acute ischemic stroke. *J Am Heart Assoc*. 2012;1:42-50

10. Sato S, Toyoda K, Uehara T, Toratani N, Yokota C, Moriwaki H, et al. Baseline nih stroke scale score predicting outcome in anterior and posterior circulation strokes. *Neurology*. 2008;70:2371-2377

11. Weimar C. Age and national institutes of health stroke scale score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: Development and external validation of prognostic models. *Stroke*. 2003;35:158-162

12. Woo D, Broderick JP, Kothari RU, Lu M, Brott T, Lyden PD, et al. Does the national institutes of health stroke scale favor left hemisphere strokes? Ninds t-pa stroke study group. *Stroke*. 1999;30:2355-2359

13. Lyden P, Claesson L, Havstad S, Ashwood T, Lu M. Factor analysis of the national institutes of health stroke scale in patients with large strokes. *Arch. Neurol.* 2004;61:1677-1680

14. Audebert HJ, Singer OC, Gotzler B, Vatankhah B, Boy S, Fiehler J, et al. Postthrombolysis hemorrhage risk is affected by stroke assessment bias between hemispheres. *Neurology*. 2011;76:629-636

15. Helenius J, Goddeau RP, Jr., Moonis M, Henninger N. Impact of leukoaraiosis burden on hemispheric lateralization of the national institutes of health stroke scale deficit in acute ischemic stroke. *Stroke*. 2016;47:24-30

16. Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, et al. Ct perfusion aspects in the evaluation of acute ischemic stroke: Thrombolytic therapy perspective. *Cerebrovascular Diseases Extra*. 2011;1:6-16

17. Alves JE, Carneiro A, Xavier J. Reliability of ct perfusion in the evaluation of the ischaemic penumbra. *The neuroradiology journal*. 2014;27:91-95

18. Fink JN, Selim MH, Kumar S, Silver B, Linfante I, Caplan LR, et al. Is the association of national institutes of health stroke scale scores and acute magnetic resonance imaging stroke volume equal for patients with right- and left-hemisphere ischemic stroke? *Stroke*. 2002;33:954-958

19. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, Heilman KM, et al. Hemispheric differences in ischemic stroke: Is left-hemisphere stroke more common? *J Clin Neurol*. 2013;9:97-102

20. Sugiura K, Muraoka K, Chishiki T, Baba M. The edinburgh-2 coma scale: A new scale for assessing impaired consciousness. *Neurosurgery*. 1983;12:411-415

21. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the nih stroke scale. *Arch Neurol*. 1989;46:660-662

22. NIH stroke scale. NINDS. https://stroke.nih.gov/resources/scale.htm Accessed April 3, 2017

23. Hunter GJ, Hamberg LM, Ponzo JA, Huang-Hellinger FR, Morris PP, Rabinov J, et al. Assessment of cerebral perfusion and arterial anatomy in hyperacute stroke with three-dimensional functional ct: Early clinical results. *AJNR Am J Neuroradiol*. 1998;19:29-37

24. Hillis AE, Wityk RJ, Barker PB, Ulatowski JA, Jacobs MA. Change in perfusion in acute nondominant hemisphere stroke may be better estimated by tests of hemispatial neglect than by the national institutes of health stroke scale. *Stroke*. 2003;34:2392-2396

25. Furtado AD, Smith WS, Koroshetz W, Dillon WP, Furie KL, Lev MH, et al. Perfusion ct imaging follows clinical severity in left hemispheric strokes. *Eur Neurol*. 2008;60:244-252

26. Fink JN, Frampton CM, Lyden P, Lees KR, Virtual International Stroke Trials Archive I. Does hemispheric lateralization influence functional and cardiovascular outcomes after stroke?: An analysis of placebo-treated patients from prospective acute stroke trials. *Stroke*. 2008;39:3335-3340

27. Yoo AJ, Romero J, Hakimelahi R, Nogueira RG, Rabinov JD, Pryor JC, et al. Predictors of functional outcome vary by the hemisphere of involvement in major ischemic stroke treated with intra-arterial therapy: A retrospective cohort study. *BMC Neurol*. 2010;10:25

28. Ween JE, Alexander MP, D'Esposito M, Roberts M. Factors predictive of stroke outcome in a rehabilitation setting. *Neurology*. 1996;47:388-392

29. Di Legge S, Saposnik G, Nilanont Y, Hachinski V. Neglecting the difference: Does right or left matter in stroke outcome after thrombolysis? *Stroke*. 2006;37:2066-2069

30. Aszalos Z, Barsi P, Vitrai J, Nagy Z. Lateralization as a factor in the prognosis of middle cerebral artery territorial infarct. *Eur Neurol*. 2002;48:141-145

Tables

Table 1. Demographics, clinical features and imaging findings in all patients and by stroke hemispheric location.

	All N=228		Left n=118		Right n=110		*P*
Age, median (IQR), y	74	(63-82)	75	(66-82)	72	(62-80)	0.27
Female sex, n (%)	142	(62.3)	75	(63.6)	67	(60.9)	0.68
Transferred, n (%)	99	(43.4)	51	(43.2)	48	(43.6)	0.95
IV rtPA-treated, n (%)	54	(23.7)	27	(22.9)	27	(24.5)	0.77
Wake-up stroke, n (%)	36	(15.8)	20	(16.9)	16	(14.5)	0.62
Time interval, median (IQR), min							
Symptoms onset to NIHSS*	196	(85-266)	194	(85-260)	200	(84-281)	0.67
NIHSS to CTP†	22	(15-35)	23	(16-41)	21	(15-31)	0.12
Symptoms onset to CTP‡	220	(118-292)	220	(114-285)	222	(129-306)	0.95
NIHSS score, median (IQR)	15	(10-18)	16	(10-20)	14	(10-17)	0.048
ASPECTS, median (IQR)	3	(2-6)	3	(3-6)	3	(1-5)	0.004
Arterial occlusion, n (%)	218	(95.6)	110	(93.2)	108	(98.2)	0.07
Site of arterial occlusion§, n (%)							0.81
Internal carotid artery	50	(22.9)	25	(22.7)	25	(23.1)	
Middle cerebral artery							
M1 segment	108	(49.5)	54	(49.1)	54	(50.0)	
M2 segment	56	(25.7)	28	(25.5)	28	(25.9)	
M3 segment	4	(1.8)	3	(2.7)	1	(0.9)	
Tandem occlusion‖, n (%)	42	(18.6)	27	(22.9)	15	(13.9)	0.08
Mismatch, n (%)	199	(87.3)	103	(87.3)	96	(87.3)	1.00
Thrombectomy, n (%)	145	(63.6)	77	(65.3)	68	(61.8)	0.59

* Excluding 36 wake-up strokes and 5 cases with missing values (3 left, 2 right).

† Three missing values (2 left, 1 right).

‡ Excluding 36 wake-up strokes and 3 cases with missing values (2 left, 1 right).

§ Excluding 10 patients without evident arterial occlusion.

‖ Two missing values (2 right).

ASPECTS: Alberta Stroke Program Early Computed Tomography Score, CTP: computed tomography perfusion, IQR: interquartile range, IV rtPA: intravenous recombinant tissue plasminogen activator, NIHSS: National Institutes of Health Stroke Scale.

Table 2. ASPECTS by stroke hemispheric location and by NIHSS score or *c-NIHSS* score 5-points strata.

	Hemispheric location	n	%	ASPECTS median	ASPECTS IQR	*P*
NIHSS score (n=228)						
≤5	Left	12	5,3	7	(6—8)	0.25
	Right	6	2,6	6	(4—7)	
6-10	Left	19	8,3	6	(5—8)	0.003
	Right	23	10,1	4	(2—5)	
11-15	Left	28	12,3	4	(3—6)	0.044
	Right	38	16,7	3	(1—5)	
16-20	Left	40	17,5	3	(1—5)	0.57
	Right	38	16,7	3	(1—5)	
>20	Left	19	8,3	3	(2—4)	0.07
	Right	5	2,2	1	(0—2)	
c-NIHSS score (n=121)						
≤5	Left	8	6,6	7	(6-8)	0.39
	Right	4	3,3	6	(5-8)	
6-10	Left	16	13,2	4	(3-6)	0.26
	Right	13	10,7	3	(2-6)	
11-15	Left	20	16,5	4	(3-5)	0.014
	Right	20	16,5	2	(2-3)	
>15	Left	20	16,5	3	(2-4)	0.81
	Right	20	16,5	3	(1-4)	

ASPECTS: Alberta Stroke Program Early Computed Tomography Score, *c-NIHSS*: corrected National Institutes of Health Stroke Scale, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale.

Table 3. NIHSS score by stroke hemispheric location, by ASPECTS strata (lower and higher than median ASPECTS) and by site of arterial occlusion (terminal ICA, M1 and M2-M3).

	Hemispheric location	NIHSS score, n=228				*c-NIHSS* score, n=121			
		n	median	(IQR)	*P*	n	median	(IQR)	*P*
ASPECTS									
≤3	Left	60	18	(14-20)	<0.001	33	14	(11-17)	0.77
	Right	66	15	(12-17)		36	15	(12-17)	
>3	Left	58	11	(7-19)	0.93	31	10	(6-15)	0.44
	Right	44	12	(8-17)		21	13	(7-17)	
Site of arterial occlusion									
Internal carotid artery	Left	25	17	(14-20)	0.048	13	14	(11-16)	0.45
	Right	25	15	(13-17)		13	15	(12-18)	
MCA M1 segment	Left	54	17	(12-20)	0.007	32	15	(10-17)	0.97
	Right	54	15	(10-17)		32	14	(10-17)	
MCA M2 or M3 segments	Left	28	10	(7-19)	0.84	16	10	(6-15)	0.35
	Right	28	12	(7-17)		11	14	(7-17)	

ASPECTS: Alberta Stroke Program Early Computed Tomography Score; *c-NIHSS***:** corrected National Institutes of Health Stroke Scale; MCA: middle cerebral artery; NIHSS: National Institutes of Health Stroke Scale.

Table 4. Demographics, clinical features and imaging findings by age strata.

	<75 years n=118		≥75 years n=110		*P*
Female sex, n (%)	65	(55.1)	77	(70.0)	0.020
Transferred, n (%)	59	(50.0)	40	(36.4)	0.038
IV rtPA-treated, n (%)	35	(29.7)	19	(17.3)	0.028
Wake-up stroke, n (%)	18	(15.3)	18	(16.4)	0.82
Time, median (IQR), min					
Symptoms onset to NIHSS*	193	(74-271)	196	(90-266)	0.77
NIHSS to CTP†	20	(14-31)	26	(17-41)	0.003
Symptoms onset to CTP‡	220	(99-303)	223	(133-287)	0.55
Left hemisphere stroke, n (%)	57	(48.3)	61	(55.5)	0.28
NIHSS score, median (IQR)	13	(9-17)	16	(11-20)	0.001
Left ($n_{<75y}$=57, $n_{\geq 75y}$=61)	13	(9-19)	17	(12-20)	0.019
Right ($n_{<75y}$=61, $n_{\geq 75y}$=49)	13	(9-16)	16	(11-18)	0.021
ASPECTS, median (IQR)	3	(2-6)	3	(2-6)	0.80
Left ($n_{<75y}$=57, $n_{\geq 75y}$=61)	4	(2-7)	3	(3-6)	0.83
Right ($n_{<75y}$=61, $n_{\geq 75y}$=49)	3	(1-5)	3	(1-6)	0.89
Arterial occlusion, n (%)	115	(93.8)	105	(95.5)	0.91
Site of arterial occlusion§, n (%)					0.98
Internal carotid artery	27	(23.9)	23	(21.9)	
Middle cerebral artery					
M1 segment	56	(49.6)	52	(49.5)	
M2 segment	28	(24.8)	28	(26.7)	
M3 segment	2	(1.8)	2	(1.9)	
Tandem lesion‖, n (%)	27	(22.9)	15	(14.5)	0.11
Mismatch, n (%)	100	(84.7)	99	(90.0)	0.23
Thrombectomy, n (%)	74	(62.7)	71	(64.5)	0.77

* Excluding 36 wake-up strokes and 5 cases with missing values (4 <75y, 1 +75y).

† Three missing values (3 <75y).

‡ Excluding 36 wake-up strokes and 3 cases with missing values (2 <75y, 1 +75y).

§ Excluding 10 patients without evident arterial occlusion.

‖ Two missing values (2 +75y)

ASPECTS: Alberta Stroke Program Early Computed Tomography Score, CTP: computed tomography perfusion, IQR: interquartile range, IV rtPA: intravenous recombinant tissue plasminogen activator, NIHSS: National Institutes of Health Stroke Scale.

Figures

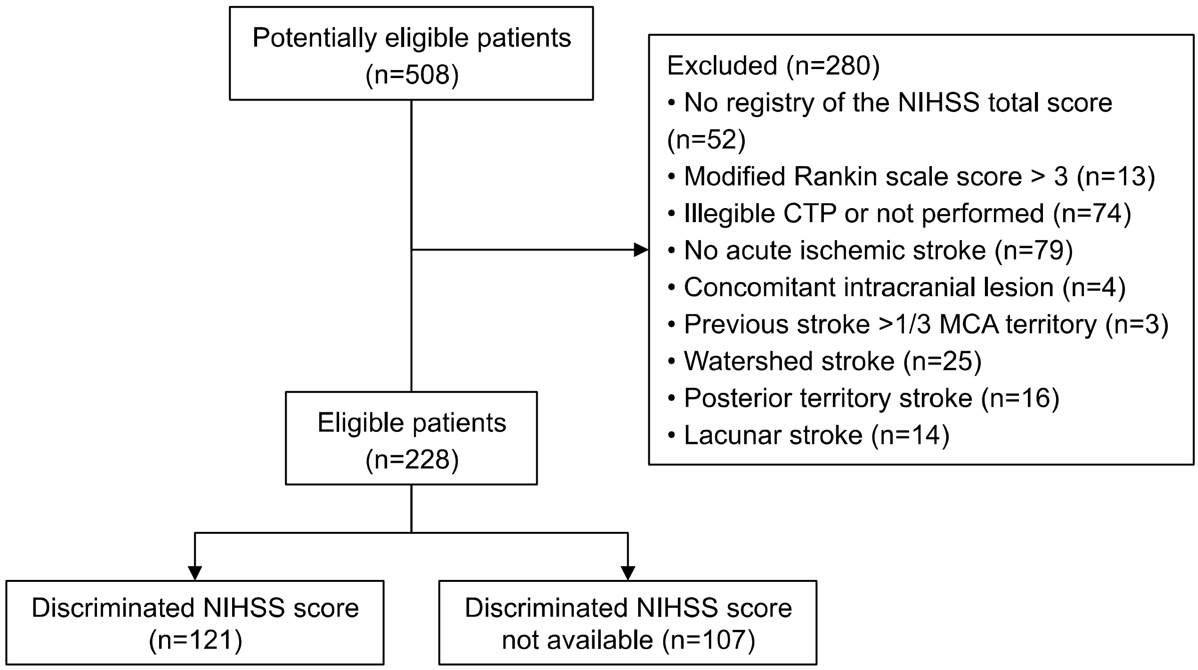

Figure 1. Algorithm of patients' selection. CTP: computed tomography perfusion, MCA: middle cerebral artery, NIHSS: National Institutes of Health Stroke Scale.

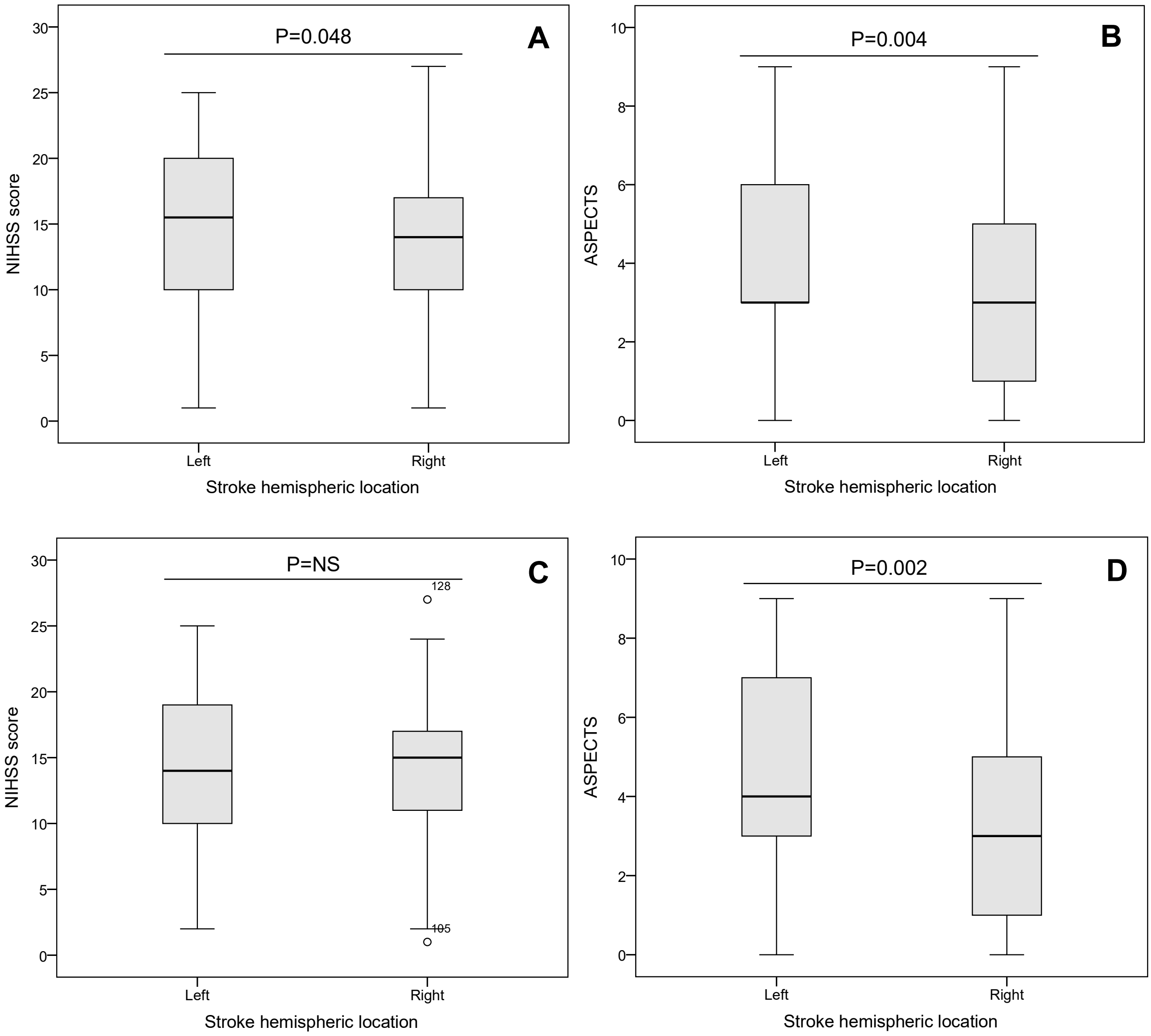

Figure 2. NIHSS score and ASPECTS by stroke hemispheric location (left vs. right): (**A** and **B**) All patients (n_{Left}=118, n_{Right}=110); (**C** and **D**) Patients within time window for thrombolysis (n_{Left}=65, n_{Right}=65).

Supplemental table 1. Demographics, clinical features and imaging findings in rtPA-treated patients compared to non-treated patients.

	Non-treated n=174		rtPA-treated n=54		*P*
Age, median (IQR), y	76	(66-82)	69	(56-80)	0.010
Female sex, n (%)	112	(64.4)	30	(55.6)	0.24
Transferred, n (%)	46	(26.4)	53	(98.1)	<0.001
Wake-up stroke, n (%)	36	(20.7)	0	(0.0)	<0.001
Time interval, median (IQR), min					
Symptoms onset to NIHSS*	152	(61-240)	249	(196-306)	<0.001
NIHSS-to-CTP time†	185	(95-268)	270	(213-326)	<0.001
Symptoms-onset-to-CTP‡	26	(18-38)	15	(12-21)	<0.001
Left hemisphere stroke, n (%)	91	(52.3)	27	(50.0)	0.77
NIHSS score, median (IQR)	15	(10-18)	15	(10-19)	0.78
ASPECTS, median (IQR)	3	(2-6)	3	(2-5)	0.34
Arterial occlusion, n (%)	167	(96.0)	51	(94.4)	0.63
Site of arterial occlusion§, n (%)					0.10
Internal carotid artery	42	(25.1)	8	(15.7)	
Middle cerebral artery					
M1 segment	75	(44.9)	33	(64.7)	
M2 segment	47	(28.1)	9	(17.6)	
M3 segment	3	(1.8)	1	(2.0)	
Tandem lesions‖, n (%)	34	(19.7)	8	(15.1)	0.46
Mismatch, n (%)	151	(86.8)	48	(88.9)	0.69
Thrombectomy, n (%)	105	(60.3)	40	(74.1)	0.07

* Excluding 36 wake-up strokes and 5 cases with missing values (4 non-treated, 1 rtPA-treated).
† Three missing values (3 non-treated).
‡ Excluding 36 wake-up strokes and 3 cases with missing values (2 non-treated, 1 rtPA-treated).
§ Excluding 10 patients without evident arterial occlusion.
‖ Two missing values (1 non-treated, 1 rtPA-treated).
ASPECTS: Alberta Stroke Program Early Computed Tomography Score, CTP: computed tomography perfusion, IQR: interquartile range, IV rtPA: intravenous recombinant tissue plasminogen activator, NIHSS: National Institutes of Health Stroke Scale.

Supplemental table 2. – Spearman's correlation coefficients of ASPECTS with NIHSS score and with *c-NIHSS* score, in eligible patients (n=228) and in patients with discriminated NIHSS score (n=121).

		Eligible patients		Patients with discriminated NIHSS score			
		NIHSS score		NIHSS score		*c-NIHSS* score	
		r_s	*P*	r_s	*P*	r_s	*P*
ASPECTS	All	-0.358	<0.001	-0.352	<0.001	-0.389	<0.001
	Left	-0.491	<0.001	-0.467	<0.001	-0.453	<0.001
	Right	-0.264	0.005	-0.325	0.014	-0.298	0.024

ASPECTS: Alberta Stroke Program Early CT Score, *c-NIHSS*: corrected National Institutes of Health Stroke Scale, NIHSS: National Institutes of Health Stroke Scale.

Supplemental table 3. Characteristics of the patients with the discriminated NIHSS score, by stroke hemispheric location.

	All n=121		Left n=64		Right n=57		*P*
Age, median (IQR), y	74	(63-82)	75	(65-81)	72	(63-82)	0.77
Female sex, n (%)	82	(67.8)	43	(67.2)	39	(68.4)	0.89
NIHSS score, median (IQR)	15	(10-18)	15	(11-20)	14	(9-17)	0.11
c-NIHSS score, median (IQR)	14	(9-16)	13	(9-16)	14	(10-17)	0.22
ASPECTS, median (IQR)	3	(2-5)	3	(3-6)	3	(2-5)	0.011
Arterial occlusion, n (%)	117	(95.6)	61	(93.2)	56	(98.2)	0.07
Site of arterial occlusion*, n (%)							0.54
Internal carotid artery	26	(22.2)	13	(21.3)	13	(23.2)	
Middle cerebral artery							
M1 segment	64	(54.7)	32	(52.5)	32	(57.1)	
M2 segment	25	(21.4)	14	(23.0)	11	(19.6)	
M3 segment	2	(1.7)	2	(3.3)	0	(0.0)	
Tandem lesion, n (%)	19	(15.7)	15	(23.4)	4	(7.0)	0.013
Mismatch, n (%)	109	(90.1)	57	(89.1)	52	(91.2)	0.69

* Four missing values (3 Left, 1 right), without arterial occlusion.
ASPECTS: Alberta Stroke Program Early Computed Tomography Score, *c*-NIHSS: *corrected* National Institutes of Health Stroke Scale, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale.

Supplemental table 4. Mean item score by stroke hemispheric location.

NIHSS or *c-NIHSS* item		Left n=64	Right n=57	*P*
1a.	Level of consciousness	0.16	0.19	0.75
1b.	Level of consciousness questions	1.58	0.30	<0.001
1c.	Level of consciousness commands	0.98	0.09	<0.001
2.	Best gaze	0.67	1.16	0.001
3.	Visual fields	1.50	1.47	0.99
4.	Facial palsy	1.50	1.72	0.07
5.	Motor arm	2.31	2.79	0.041
6.	Motor leg	2.03	2.25	0.34
7.	Limb ataxia	0.03	0.00	0.35
8.	Sensory	0.91	1.05	0.24
9.	Best language	1.83	0.05	<0.001
10.	Dysarthria	1.23	0.98	0.025
11.	Extinction and inattention	0.00	1.18	<0.001
c-11.	c-Extinction and inattention	0.00	1.69	<0.001

Since the range of scores for each item was narrow, we used the mean score to describe these data.

c-NIHSS: *corrected* National Institutes of Health Stroke Scale, NIHSS: National Institutes of Health Stroke Scale.